

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 13 June 2000 (13.06.00)	
International application No. PCT/EP99/06980	Applicant's or agent's file reference PM 134-GL
International filing date (day/month/year) 21 September 1999 (21.09.99)	Priority date (day/month/year) 24 September 1998 (24.09.98)
Applicant BISOGNO, Tiziana et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
19 April 2000 (19.04.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer S. Mafla
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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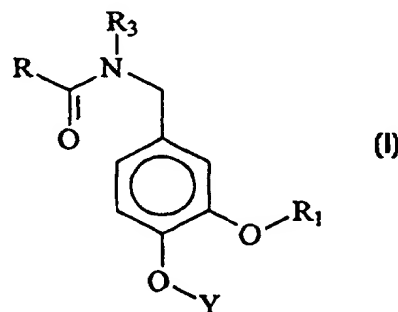
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/165, A61P 29/00, 31/00		A3	(11) International Publication Number: WO 00/16756
			(43) International Publication Date: 30 March 2000 (30.03.00)
(21) International Application Number: PCT/EP99/06980 (22) International Filing Date: 21 September 1999 (21.09.99) (30) Priority Data: MI98A002064 24 September 1998 (24.09.98) IT (71) Applicants (for all designated States except US): INNOVET ITALIA S.R.L. [IT/IT]; Via Egadi, 7, I-20144 Milano (IT). CONSIGLIO NAZIONALE DELLE RICERCHE [IT/IT]; Piazzale Aldo Moro, 5, I-00185 Roma (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): BISOGNO, Tiziana [IT/IT]; Istituto per la Chimica di Molecole di Interesse Biologico - CNR, Via Toiano, 6, I-80078 Arco Felice (IT). DELLA VALLE, Francesco [IT/IT]; Via Cerato, 14, I-35122 Padova (IT). DE PETROCELLIS, Luciano [IT/IT]; Istituto di Cibernetica - CNR, Via Toiano, 6, I-80078 Arco Felice (IT). DI MARZO, Vincenzo [IT/IT]; Istituto per la Chimica di Molecole di Interesse Biologico - CNR, Via Toiano, 6, I-80078 Arco Felice (IT). MARCOLONGO, Gabriele [IT/IT]; Via Strade Interne, 3, I-35020 Due Carrare-Padova (IT). MELCK, Dominique [IT/IT]; Istituto per la Chimica di Molecole di Interesse Biologico - CNR, Via Toiano, 6, I-80078 Arco Felice (IT).		(74) Agents: LONG, Giorgio et al.; Jacobacci & Perani S.p.A., Via Visconti di Modrone, 7, I-20122 Milano (IT). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. (88) Date of publication of the international search report: 8 September 2000 (08.09.00)	

(54) Title: USE OF N-ACYLVANILLINAMIDE DERIVATIVES AS AGONISTS OF PERIPHERAL CANNABINOID CB1 RECEPTORS

(57) Abstract

The present invention relates to the use of N-acylvanillinamide derivatives capable of activating the peripheral receptor CB1 of cannabinoids. In particular, the present invention relates to the use of compounds of general formula (I), in which the meanings of R, R₁, R₃ and Y are as defined in the description, for the preparation of a medicinal product which is capable of activating the peripheral receptor CB1 of cannabinoids.



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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/06980

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/165 A61P29/00 A61P31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	MELCK D ET AL: "Unsaturated long-chain N-acyl-vanillyl-amides (N-AVAMs): vanilloid receptor ligands that inhibit anandamide-facilitated transport and bind to CB1 cannabinoid receptors." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1999 AUG 19) 262 (1) 275-84. , XP000892119 the whole document	1-21
P, X	DI MARZO V ET AL: "Interactions between synthetic vanilloids and the endogenous cannabinoid system." FEBS LETTERS, (1998 OCT 9) 436 (3) 449-54. , XP000892132 the whole document	1-21

-/-

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

16 May 2000

Date of mailing of the international search report

25/05/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Orviz Diaz, P

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/06980

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	<p>DRAY A: "NEUROPHARMACOLOGICAL MECHANISMS OF CAPSAICIN AND RELATED SUBSTANCES" BIOCHEMICAL PHARMACOLOGY, GB, PERGAMON, OXFORD, vol. 44, no. 4, 18 August 1992 (1992-08-18), pages 611-615, XP000576776 ISSN: 0006-2952 the whole document</p>	5-7
X,Y	<p>WINTER J. ET AL: "Characterization of resiniferatoxin binding sites on sensory neurons: Co-regulation of resiniferatoxin binding and capsaicin sensitivity in adult rat dorsal root ganglia." NEUROSCIENCE, (1993) 57/3 (747-757). , XP000905278 the whole document</p>	5-7
X,Y	<p>MORRE D J ET AL: "Capsaicin inhibits plasma membrane NADH oxidase and growth of human and mouse melanoma lines." EUROPEAN JOURNAL OF CANCER, (1996 OCT) 32A (11) 1995-2003. , XP000905279 the whole document</p>	5-7
X	<p>DATABASE WPI Section Ch, Week 199318 Derwent Publications Ltd., London, GB; Class B03, AN 1993-149228 XP002137845 & JP 05 086086 A (OGAWA KORYO KK), 6 April 1993 (1993-04-06) abstract</p>	11-16
X	<p>DATABASE WPI Section Ch, Week 199815 Derwent Publications Ltd., London, GB; Class B03, AN 1998-162352 XP002137846 & JP 10 025237 A (KANEBO LTD), 27 January 1998 (1998-01-27) abstract</p>	11-16
A	<p>WO 96 18391 A (LIFEGROUP SPA ; DELLA VALLE FRANCESCO (IT); LEON ALBERTA (IT); MARC) 20 June 1996 (1996-06-20) cited in the application claims; examples 20,21</p>	1-21

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No


PCT/EP 99/06980

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
JP 5086086	A	06-04-1993	NONE		
JP 10025237	A	27-01-1998	NONE		
WO 9618391	A	20-06-1996	IT	MI942512 A	14-06-1996
			AU	4344296 A	03-07-1996
			CA	2207850 A	20-06-1996
			EP	0799033 A	08-10-1997
			JP	11500411 T	12-01-1999
			US	5990170 A	23-11-1999

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PM 134-GL		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP99/06980	International filing date (day/month/year) 21/09/1999	Priority date (day/month/year) 24/09/1998	
International Patent Classification (IPC) or national classification and IPC A61K31/00			
Applicant INNOVET ITALIA S.R.L. et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 6 sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none">I <input checked="" type="checkbox"/> Basis of the reportII <input type="checkbox"/> PriorityIII <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicabilityIV <input type="checkbox"/> Lack of unity of inventionV <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statementVI <input type="checkbox"/> Certain documents citedVII <input type="checkbox"/> Certain defects in the international applicationVIII <input type="checkbox"/> Certain observations on the international application			
Date of submission of the demand 19/04/2000		Date of completion of this report 18.12.2000	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Escolar Blasco, P Telephone No. +49 89 2399 7331	



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP99/06980

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-57 as originally filed

Claims, No.:

1-21 with telefax of 04/12/2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP99/06980

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-21
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/06980

Comments on item V

1. Reference is made to the following documents:

D1: DATABASE WPI Section Ch, Week 199318, AN 1993-149228 & JP 05 086086 A

D2: DATABASE WPI Section Ch, Week 199815, AN 1998-162352 & JP 10 025237 A

D3: DRAY A: 'Neuropharmacological mechanisms of capsaicin and related substances' BIOCHEMICAL PHARMACOLOGY, vol. 44, no. 4, 18 August 1992, pages 611-615

D4: WINTER J. ET AL: 'Characterization of resiniferatoxin binding sites on sensory neurons: Co-regulation of resiniferatoxin binding and capsaicin sensitivity in adult rat dorsal root ganglia.' NEUROSCIENCE, (1993) 57/3 (747-757)

D5: MORRE D J ET AL: 'Capsaicin inhibits plasma membrane NADH oxidase and growth of human and mouse melanoma lines.' EUROPEAN JOURNAL OF CANCER, (1996 OCT) 32A (11) 1995-2003

D6: WO 96 18391 A

2. Claims 1-4 refer to the use of known products (the derivatives of formula I) for the preparation of a medicinal product for treating pathologies characterised by a high degree of cellular and tissue hyperreactivity mediated by supramaximal levels of nerve growth factor. Several documents disclose the use in medicine of compounds falling within the scope of claims 1-4 (see the abstract of D1; p.613, right col. in D3; p. 747, left column, first paragraph in D4; the abstract of D5 and examples 20 and 21 in D6), but none of them relates to the activation of the CB1 receptor nor to hyperreactivity disorders.

The disclaimer included in claim 1 is due to the fact that D3 mentions rheumatoid arthritis and D5 certain types of melanoma and carcinoma, these diseases being of hyperreactive nature. However, neither D3 nor D5 give any hint about other possible uses of the compounds cited. In view of these documents, the skilled person could not deduce that such compounds activate the CB1 receptor, and he would not either think of using them for the treatment of other hyperreactive disorders.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/06980

2.1 Dependent claims 5-10 are allowable.

3. The compounds of claims 11-12, 15-16 and the methods of claims 13-14 have been rendered novel over D1 and D2 again through a disclaimer. The overlap between both general formulae not being there anymore, novelty can be acknowledged.

An inventive step seems also to be present, as the modification done to the derivatives disclosed in D1-D2 leads to compounds having a different activity than the ones of claims 11-12 (as already said in section 2, these documents do not contain any suggestion of CB1 receptor activation or treatment of hyperreactivity disorders).

4. Having regard to the present prior art, the subject-matter of claims 17-21, i.e. the combination of the compounds of formula (I) with CB2 agonists, is also novel and inventive. The description shows a synergistic effect of this combination.

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PM 134-GL	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 99/ 06980	International filing date (day/month/year) 21/09/1999	(Earliest) Priority Date (day/month/year) 24/09/1998
Applicant INNOVET ITALIA S.R.L. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the International search was carried out on the basis of the International application in the language in which it was filed, unless otherwise indicated under this item.

☐ the International search was carried out on the basis of a translation of the International application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the International application, the International search was carried out on the basis of the sequence listing:

☐ contained in the International application in written form.

☐ filed together with the International application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the International application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

USE OF N-ACYLVANILLINAMIDE DERIVATIVES AS AGONISTS OF PERIPHERAL CANNABINOID CB1 RECEPTORS

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/06980

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/165 A61P29/00 A61P31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	MELCK D ET AL: "Unsaturated long-chain N-acyl-vanillyl-amides (N-AVAMs): vanilloid receptor ligands that inhibit anandamide-facilitated transport and bind to CB1 cannabinoid receptors." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1999 AUG 19) 262 (1) 275-84. , XP000892119 the whole document	1-21
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-/-



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

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- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "A" document member of the same patent family

Date of the actual completion of the international search

16 May 2000

Date of mailing of the international search report

25/05/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Orviz Diaz, P

INTERNATIONAL SEARCH REPORT

International Application No

CT/EP 99/06980

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	DRAY A: "NEUROPHARMACOLOGICAL MECHANISMS OF CAPSAICIN AND RELATED SUBSTANCES" BIOCHEMICAL PHARMACOLOGY, GB, PERGAMON, OXFORD, vol. 44, no. 4, 18 August 1992 (1992-08-18), pages 611-615, XP000576776 ISSN: 0006-2952 the whole document	5-7
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X,Y	MORRE D J ET AL: "Capsaicin inhibits plasma membrane NADH oxidase and growth of human and mouse melanoma lines." EUROPEAN JOURNAL OF CANCER, (1996 OCT) 32A (11) 1995-2003. , XP000905279 the whole document	5-7
X	DATABASE WPI Section Ch, Week 199318 Derwent Publications Ltd., London, GB; Class B03, AN 1993-149228 XP002137845 & JP 05 086086 A (OGAWA KORYO KK), 6 April 1993 (1993-04-06) abstract	11-16
X	DATABASE WPI Section Ch, Week 199815 Derwent Publications Ltd., London, GB; Class B03, AN 1998-162352 XP002137846 & JP 10 025237 A (KANEBO LTD), 27 January 1998 (1998-01-27) abstract	11-16
A	WO 96 18391 A (LIFEGROUP SPA ; DELLA VALLE FRANCESCO (IT); LEON ALBERTA (IT); MARC) 20 June 1996 (1996-06-20) cited in the application claims; examples 20,21	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/06980

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
JP 5086086	A	06-04-1993	NONE		
JP 10025237	A	27-01-1998	NONE		
WO 9618391	A	20-06-1996	IT	MI942512 A	14-06-1996
			AU	4344296 A	03-07-1996
			CA	2207850 A	20-06-1996
			EP	0799033 A	08-10-1997
			JP	11500411 T	12-01-1999
			US	5990170 A	23-11-1999